1644 #13 gnd

Dkt. 69772-PCT-US/JPW/GJG/CSM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rina Aharoni et al. Examiner: A. De Cloux

U.S. Serial No.: 09/768,872 Group Art Unit: 1644

Filed : January 23, 2001

For : TREATMENT OF AUTOIMMUNE CONDITIONS WITH COPOLYMER 1 RELATED COPOLYMERS AND PEPTIDES.

1185 Avenue of the Americas
New York, New York 10036
June 26, 2002

Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

INFORMATION DISCLOSURE STATEMENT
PURSUANT TO 37 C.F.R. §1.97(b)(3)

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following Reference Items 1-159 **(Exhibits 1-149)** which are listed again on the accompanying Form PTO-1449 **(Exhibit A)**. Applicants request that the Examiner review the references and make them of record in the subject application.

This Information Disclosure Statement is being submitted before the issuance of a first Office Action on the merits in connection with the subject application. Accordingly, no fee is required and this Information Disclosure Statement shall be considered pursuant to 37 C.F.R. §1.97(b)(3).

For the convenience of the Examiner, applicants point out that Reference Item 108 was cited in the October 29, 1999 International Search Report in the corresponding PCT International Application, and a copy of the Report is enclosed as **Exhibit B**.

Applicants also point out that several of the listed references are

Applicants also point out that several of the listed references are counterparts of each other and are cumulative. Therefore, in accordance with 37 C.F.R. § 1.98(c), a counterpart of a reference is identified after the cite to the reference, but a copy of only one of the counterparts is being provided. Applicants will provide the Examiner with copies of any reference upon request.

1. U.S. Patent No. 3,849,550, issued November 19, 1974 (Teitelbaum, et al.) **(Exhibit 1)**;

2. U.S. Patent No. 4,339,431, issued July 13, 1982 (Gaffar) **(Exhibit 2)**;

3. U.S. Patent No. 5,204,099, issued April 20, 1993 (Barbier, et al.) **(Exhibit 3)**;

4. U.S. Patent No. 5,591,629, issued January 7, 1997 (Rodriguez et al.) **(Exhibit 4)**;

5. U.S. Patent No. 5,627,206, issued May 6, 1997 (Hupe, et al.) **(Exhibit 5)**;

6. U.S. Patent No. 5,668,117, issued September 16, 1997 (Shapiro et al.) **(Exhibit 6)**;

7. U.S. Patent No. 5,719,296, issued February 17, 1998 (Acton, III, et al.) **(Exhibit 7)**;

8. U.S. Patent No. 5,800,808, issued September 1, 1998 (Konfino, et al.) **(Exhibit 8)**;

9. U.S. Patent No. 5,858,964, issued January 12, 1999 (Aharoni, et al.) **(Exhibit 9)**;

10. U.S. Patent No. 5,981,589, issued November 9, 1999 (Konfino, et al.) **(Exhibit 10)**;

11. U.S. Patent No. 5,958,972, issued September 28, 1999 (Hupe, et al.) **(Exhibit 11)**;

12. U.S. Patent No. 6,048,898, issued April 11, 2000 (Konfino, et al.) **(Exhibit 12)**;

13. U.S. Patent No. 6,054,430, issued April 25, 2000 (Konfino, et al.) **(Exhibit 13)**;

14. U.S. Patent No. 6,214,791, issued April 10, 2001 (Arnon, et al.) **(Exhibit 14)**;

15. U.S. Patent No. 6,342,476, issued January 29, 2002 (Konfino, et al.) **(Exhibit 15)**;

16. U.S. Patent Publication No. US-2001-0055568-A1, published December 27, 2001 (Gilbert et al.) **(Exhibit 16)**;

17. U.S. Serial No. 09/359,099, filed July 22, 1999 (Strominger et al.) **(Exhibit 17)**;

18. U.S. Serial No. 09/405,743, filed September 24, 1999 (Gad et al.) **(Exhibit 18)**;

19. U.S. Serial No. 09/816,989, filed March 23, 2001 (Gad et al.). Applicants point out that this reference is a counterpart of U.S. Serial No. 09/405,743(Exhibit 18);

20. U.S. Serial No. 09/875,429, filed June 5, 2001 (Yong and Chabot) **(Exhibit 19)**;

21. U.S. Serial No. 09/885,227, filed June 20, 2001 (Rodriguez and Ure) **(Exhibit 20)**;

22. PCT International Application No. PCT/US88/02139 (WO 88/10120), published December 29, 1988 (Weiner et al.) **(Exhibit 21)**;

23. PCT International Application No. PCT/US95/06551 (WO 95/31990), published November 30, 1995 (Konfino et al.). Applicants point out that this reference is a counterpart of U.S. Patents Nos. 5,800,808 (Exhibit 8) and 6,342,476 (Exhibit 15);

24. PCT International Application No. PCT/EP95/02125 (WO/95/33475), published December 14, 1995 (Kott et al.) **(Exhibit 22)**;

25. PCT International Application No. PCT/US98/00375 (WO 98/30227), published July 16, 1998 (Arnon et al.). Applicants point out that this reference is a counterpart of US Patent No. 6,214,791 (Exhibit 14);

26. PCT International Application No. PCT/US99/16617 (WO 00/05249)

published February 3, 2000 (Strominger et al). Applicants point out that this reference is a counterpart of U.S. Serial No. 09/359,099 (Exhibit 17);

27. PCT International Application No. PCT/US99/16747 (WO 00/05250) published February 3, 2000 (Aharoni et al.). Applicants point out that this reference is a counterpart of the subject application;

28. PCT International Application No. PCT/US99/22402 (WO 00/18794) published April 6, 2000 (Gad, et al.). Applicants point out that this reference is a counterpart of U.S. Serial No. 09/405,743 (Exhibit 18) and U.S. Serial No. 09/816,989;

29. PCT International Application No. PCT/US99/22836 (WO 00/20010) published April 13, 2000 (Flechter, et al.) **(Exhibit 23)**;

30. PCT International Application No. PCT/US99/27107 (WO 00/27417) published May 18, 2000 (Aharoni et al.)**(Exhibit 24)**;

31. PCT International Application No. PCT/US01/05198 (WO 01/60392) published August 23, 2001 (Gilbert et al.) Applicants point out that this reference is a counterpart of U.S. Patent Publication No. US-2001-0055568-A1 (Exhibit 16);

32. PCT International Application No. PCT/US01/18248 (WO 01/93828) published December 13, 2001 (Yong and Chabot). Applicants point out that this reference is a counterpart of U.S. Serial No. 09/875,429 (Exhibit 19);

33. PCT International Application No. PCT/US01/19649 (WO 01/97846) published December 27, 2001 (Rodriguez and Ure). Applicants point out that this reference is a counterpart of U.S. Serial

No. 09/885,227 (Exhibit 20);

34. European Patent Application No. 0 383 620 A2, published August 22, 1990 (Cook) **(Exhibit 25)**;

35. European Patent No. 0 359 783 B1, published November 29, 1995 (Werner, et al.);

36. Teitelbaum, et al., "Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Polypeptide", Eur. J. Immunol., 1971, 1, 242-248 **(Exhibit 26)**;

37. Teitelbaum, et al., "Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Polypeptide", Israel J. Med. Sci., 1971, 7, 630-631 (Abstract) **(Exhibit 27)**;

38. Arnon, et al., "Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Copolymer Immunological Cross Reactive with Basic Encephalitogen", Israel J. Med. Sci., 1972, 8, 1759-1760 **(Exhibit 28)**;

39. Teitelbaum, et al., "Protection Against Experimental Allergic Encephalomyelitis", Nature, 1972, 240, 564-566 **(Exhibit 29)**;

40. Webb, et al., "Further Studies on the Suppression of Experimental Allergic Encephalomyelitis by Synthetic Copolymer", Israel J. Med. Sci., 1972, 8, 656-657 **(Exhibit 30)**;

41. Teitelbaum, et al., "Suppression of Experimental Allergic Encephalomyelitis with Basic Polymers", Eur. J. Immunol.,

1973, 3, 273-279 **(Exhibit 31)**;

42. Webb, et al., "In Vivo and in Vitro Immunological Cross-reactions between Basic Encephalitogen and Synthetic Basic Polypeptides Capable of Suppressing Experimental Allergic Encephalomyelitis", Eur. J. Immunol., 1973, 3, 279-286 **(Exhibit 32)**;

43. Teitelbaum, et al., "Dose-response Studies on Experimental Allergic Encephalomyelitis Suppression by COP-1", Israel J. Med. Sci., 1974, 10(9), 1172-1173 **(Exhibit 33)**;

44. Teitelbaum, et al., "Suppression of Experimental Allergic Encephalomyelitis in Rhesus Monkeys by a Synthetic Basic Copolymer", Clin. Immunol. Immunopath., 1974, 3, 256-262 **(Exhibit 34)**;

45. Webb, et al., "Suppression of Experimental Allergic Encephalomyelitis in Rhesus Monkeys by a Synthetic Basic Copolymer", Isr. J. Med. Sci., 1975, 11, 1388 (Abstract) **(Exhibit 35)**;

46. Webb, et al., "Molecular Requirements Involved in Suppression of EAE by Synthetic Basic Copolymers of Amino Acids", Immunochem., 1976, 13, 333-337 **(Exhibit 36)**;

47. Abramsky, et al., "Effect of a Synthetic Polypeptide (COP-1) on Patients with Multiple Sclerosis and with Acute Disseminated Encephalomyelitis", J. Neurol. Sci., 1977, 31, 433-438 **(Exhibit 37)**;

48. Teitelbaum, et al., "Suppression of Experimental Allergic Encephalomyelitis in Baboons by Cop 1", Israel J. Med. Sci., 1977, 13, 1038 (Abstract) **(Exhibit 38)**;

49. Arnon, et al., "Suppression of EAE in Baboons by a Synthetic Polymer of Amino Acids", Neurol., 1978, 28, 336 (Abstract) **(Exhibit 39)**;

50. Sela, et al., "Experimental Allergic Encephalomyelitis" in Menarini Series on Immunopathology, vol. 1, First Symposium of Organ Specific Autoimmunity", Cremona, Italy, June, 1977, (Miescher P.A. ed., Schwabe Co., Basel, 1978), 9-21 **(Exhibit 40)**;

51. Alvord, et al., "Myelin Basic Protein Treatment of Experimental Allergic Encephalomyelitis in Monkeys", Ann. Neurol., 1979, 6, 469-473 **(Exhibit 41)**;

52. Keith, et al., "The Effect of COP 1, a Synthetic Polypeptide, on Chronic Relapsing Experimental Allergic Encephalomyelitis in Guinea Pigs" J. Neurol. Sci., 1979, 42, 267-274 **(Exhibit 42)**;

53. Lando, et al., "Effect of Cyclophosphamide on Suppressor Cell Activity in Mice Unresponsive to EAE", J. Immunol., 1979, 123, 2156-2160. (Abstract) **(Exhibit 43)**;

54. Lando, et al., "Experimental Allergic Encephalomyelitis in Mice - Suppression and Prevention with COP-1", Israel J. Med. Sci., 1979, 15, 868-869 (Abstract) **(Exhibit 44)**;

55. Teitelbaum, et al., "Blocking of Sensitization to

Encephalitogenic Basic Protein in Vitro by Synthetic Basic Copolymer (COP 1)" in Cell Biology and Immunology of Leukocyte Function (Academic Press, New York, 1979) 681-685 **(Exhibit 45)**;

56. Teitelbaum, "Suppression of Experimental Allergic Encephalomyelitis with a Synthetic Copolymer - Relevance to Multiple Sclerosis", in Humoral Immunity in Neurological Diseases (Karcher D., Lowenthal A. & Strosberg A.D., eds., Plenum Publishing Corp., 1979) 609-613 **(Exhibit 46)**;

57. Arnon, et al., "Desensitization of Experimental Allergic Encephalomyelitis with Synthetic Peptide Analogues" in The Suppression of Experimental Allergic Encephalomyelitis and Multiple Sclerosis (Academic Press, New York, 1980) 105-107 **(Exhibit 47)**;

58. Arnon, "A Synthetic Copolymer of Amino Acids in a Clinical Trial for MS Therapy" in Progress in Multiple Sclerosis Research (Bauer, Ritter, eds., Springer Verlag New York, 1980) 416-418 **(Exhibit 48)**;

59. Bornstein, et al., "Treatment of Multiple Sclerosis with a Synthetic Polypeptide: Preliminary Results", Ann. Neurol., 1980, 8, 117 (Abstract) **(Exhibit 49)**;

60. Bornstein, et al., "Treatment of Multiple Sclerosis with a Synthetic Polypeptide: Preliminary Results", Trans. Am. Neurol. Assoc., 1980, 105, 348-350 **(Exhibit 50)**;

61. McDermott, et al., "Antigen-induced Suppression of Experimental Allergic Neuritis in the Guinea Pig", J. Neurol.

Sci., 1980, 46, 137-143 **(Exhibit 51)**;

62. Arnon, "Experimental Allergic Encephalomyelitis - Susceptibility and Suppression", Immunological Rev., 1981, 55, 5-30 **(Exhibit 52)**;

63. Bornstein, et al., "Multiple Sclerosis: Trial of a Synthetic Polypeptide", Ann. Neurol., 1982, 11, 317-319 **(Exhibit 53)**;

64. Brosnan, et al., "The Response of Normal Human Lymphocytes to Copolymer 1", J. Neuropath. Exp. Neurol., 1983, 42, 356 (Abstract) **(Exhibit 54)**;

65. Lisak, et al., "Effect of Treatment with Copolymer 1 (Cop-1) on the in Vivo and in Vitro Manifestations of Experimental Allergic Encephalomyelitis (EAE)", J. Neurol. Sci., 1983, 62, 281-293 **(Exhibit 55)**;

66. Bornstein, et al., "Clinical Trials of Copolymer 1 in Multiple Sclerosis", Ann. N.Y. Acad. Sci. (USA), 1984, 366-372 **(Exhibit 56)**;

67. Bornstein, et al., "Clinical Trials of a Synthetic Polypeptide (Copolymer 1) for the Treatment of Multiple Sclerosis" in Gonsett et al., Immunological and Clinical Aspects of Multiple Sclerosis (MTP Press, The Hague, 1984) 144-150 **(Exhibit 57)**;

68. Brosnan, et al., "Copolymer 1: Effect on Normal Human Lymphocytes", Ann. N.Y. Acad. Sci. (USA), 1984, 436, 498-499 **(Exhibit 58)**;

69. Bornstein, et al., "Multiple Sclerosis: Clinical Trials of a Synthetic Polypeptide, Copolymer 1", Neurol., 1985, 35 (Suppl. 1), 103 (Abstract) **(Exhibit 59)**;

70. Brosnan, et al., "Immunogenic Potentials of Copolymer 1 in Normal Human Lymphocytes", Neurol., 1985, 35, 1754-1759 **(Exhibit 60)**;

71. Burns, et al., "Human Cellular Immune Response in Vitro to Copolymer 1 and Myelin Basic Protein (MBP)", Neurol., 1985, 35 (Suppl. 1), 170 (Abstract) **(Exhibit 61)**;

72. Teitelbaum, et al., "Monoclonal Antibodies to Myelin Basic Protein Cross React with Synthetic EAE-suppressive Copolymer, COP 1" in Proc. 7th Eur. Immunol. Mtg., Jerusalem, September 8-13, 1985 (Abstract) **(Exhibit 62)**;

73. Thompson, "MCQ Tutor: Medical Immunology Multiple Choice Questions", Immunol. Today, 1985, 6(4), 141 **(Exhibit 63)**;

74. Burns, et al., "Human Cellular Immune Response to Copolymer 1 and Myelin Basic Protein", Neurol., 1986, 36, 92-94 **(Exhibit 64)**;

75. Bornstein, "Cop 1 May be Beneficial for Patients with Exacerbating-remitting Form of Multiple Sclerosis", Adv. Ther. (USA), 1987, 4, 206 (Abstract) **(Exhibit 65)**;

76. Bornstein, et al., "A Pilot Trial of Cop 1 in Exacerbating-

remitting Multiple Sclerosis", New Eng. J. Med., 1987, 317(7), 408-414 **(Exhibit 66)**;

77. Rolak, "Copolymer-I Therapy for Multiple Sclerosis", Clin. Neuropharmacology, 1987, 10(5), 389-396 **(Exhibit 67)**;

78. Winer, "COP 1 Therapy for Multiple Sclerosis", New Eng. J. Med., 1987, 317(7), 442-444 **(Exhibit 68)**;

79. Arnon, et al., "Suppression of Demyelinating Diseases by Synthetic Copolymers", in A Multidisciplinary Approach to Myelin Disease (G. Serlupi Crescenzi, ed., Plenum Publishing Corp., 1988) 243-250 **(Exhibit 69)**;

80. Baumhefner, et al., "Copolymer 1 as Therapy for Multiple Sclerosis: The Cons", Neurol., 1988, 38(Suppl. 2), 69-71 **(Exhibit 70)**;

81. Bornstein, et al., "Clinical Experience with COP-1 in Multiple Sclerosis", Neurol., 1988, 38(Suppl. 2), 66-69 **(Exhibit 71)**;

82. Teitelbaum, et al., "Specific Inhibition of the T-cell Response to Myelin Basic Protein by the Synthetic Copolymer Cop 1", Proc. Natl. Acad. Sci. USA, 1988, 85, 9724-9728 **(Exhibit 72)**;

83. Arnon, et al., "Suppression of Experimental Allergic Encephalomyelitis by Cop-1 - Relevance to Multiple Sclerosis", Israel J. Med. Sci., 1989, 25, 686-689 **(Exhibit 73)**;

84. Bornstein, et al., "Pilot Trial of COP-1 in Chronic Progressive Multiple Sclerosis: Preliminary Report", from The International Multiple Sclerosis Conference: An Update on Multiple Sclerosis, Roma (Italy), September 15-17, 1988, in Elsevier Science Publisher, 1989, 225-232 **(Exhibit 74)**;

85. Teitelbaum, et al., "Clinical Trial of Copolymer 1 in Multiple Sclerosis" J. Israel Med. Assoc., 1989, CXVI(9), 453-456 **(Exhibit 75)**;

86. Bornstein, et al., "Clinical Trials of Cop 1 in Multiple Sclerosis" in Handbook of Multiple Sclerosis (S.D. Cook Marcel Rekker, ed., 1990) 469-480 **(Exhibit 76)**;

87. Carter, et al., "Newer Drug Therapies for Multiple Sclerosis", Drug Therapy, 1990, 31-32, 37-39, 42-43 **(Exhibit 77)**;

88. Grgacic, et al., "Cell-mediated Immune Response to Copolymer 1 in Multiple Sclerosis Measured by the Macrophage Procoagulant Activity Assay", Int. Immunol., 1990, 2(8), 713-718 **(Exhibit 78)**;

89. Kay, et al., "The Mechanism of Action of FK 506", Transplantation Proceedings, 1990, 22(1, Suppl. 1), 96-99 **(Exhibit 79)**;

90. Lee, et al., "Peptide and Protein Drug Delivery" in Advances in Parenteral Sciences (Vincent H.L. Lee, ed., Marcel Dekker, Inc., 1990) 691-695 **(Exhibit 80)**;

91. Myers, et al., "The Peculiar Difficulties of Therapeutic Trials for Multiple Sclerosis", Neurologic Clinics, 1990, 8(1), 119-141 **(Exhibit 81)**;

92. Sela, et al., "Suppressive Activity of COP-1 in EAE and its Relevance to Multiple Sclerosis", Bull. Inst. Pasteur, 1990, 88, 303-314 **(Exhibit 82)**;

93. Starzl, Transplantation Proceedings, 1990, 22 (1, Suppl. 1), 5 **(Exhibit 83)**;

94. Wender, "Copolymer 1 (COP-1) in the Treatment of Multiple Sclerosis (letter)" Neur. Neurochir. Pol., 1990, 24, 113 **(Exhibit 84)**;

95. Bornstein, et al., "A Placebo-controlled, Double-blind, Randomized Two-center, Pilot Trial of Cop 1 in Chronic Progressive Multiple Sclerosis", Neurol., 1991, 41, 533-539 **(Exhibit 85)**;

96. Burns, et al., "Failure of Copolymer 1 to Inhibit the Human T-cell Response to Myelin Basic Protein", Neurol., 1991, 41, 1317-1319, **(Exhibit 86)**;

97. Clinical Trial Protocol No. 9001, Teva Pharmaceutical Industries, Ltd., first patient enrolled October 23, 1991 **(Exhibit 87)**;

98. Ferrara, et al., "Graft-Versus-Host Disease", New Eng. J.

Med., 1991, 324, 667-674 **(Exhibit 88)**;

99. Meiner, "COP-1 Multicenter Clinical Trial in Exacerbating-remitting Multiple-Sclerosis: One Year Follow-up", J. Neurol., 1991(Suppl. 1) (Abstract) **(Exhibit 89)**;

100. Rothbard, et al., "Interactions Between Immunogenic Peptides and MHC Proteins", Ann. Rev. Immunol., 1991, 9, 527-565 **(Exhibit 90)**;

101. Salvetti, et al., "Myelin Basic Protein T Cell Epitopes in Patients with Multiple Sclerosis", Department of Neurological Sciences, University of Rome, La Sapienza 1991, 72 (Abstract) **(Exhibit 91)**;

102. Teitelbaum, et al., "Cross-reactions and Specificities of Monoclonal Antibodies Against Myelin Basic Protein and Against the Synthetic Copolymer 1", Proc. Natl. Acad. Sci. (USA), 1991, 88, 9528-9532 **(Exhibit 92)**;

103. Van den Bogaerde, et al., "Induction of Long-Term Survival of Hamster Heart Xenografts in Rats", Transplantation, 1991, 52, 15-20 **(Exhibit 93)**;

104. Bornstein, et al., "Treatment of Multiple Sclerosis with Copolymer 1" in Treatment of Multiple Scleorsis: Trial Design, Results and Future Perspectives (Rudick R.A. & Goodkin D.E., eds., Springer Verlag, London, 1992) 173-198 **(Exhibit 94)**;

105. Johnson, "Clinical Studies in Copolymer 1 Therapy for Exacerbating-remitting Multiple Sclerosis", in Congress for Advances in the Understanding and Treatment of Multiple

Sclerosis, Boston (USA), Oct. 28-29, 1992 **(Exhibit 95)**;

106. Milo, et al., "Inhibition of Myelin Basic Protein-specific Human T-cell Lines by COP-1", Israel J. Med. Sci., 1992, 28, 486 (Abstract) **(Exhibit 96)**;

107. Racke, et al., "Copolymer-1-induced Inhibition of Antigen-specific T Cell Activation: Interference with Antigen Presentation", J. Neuroimmunol., 1992, 37, 75-84 **(Exhibit 97)**;

108. Teitelbaum, et al., "Synthetic Copolymer 1 Inhibits Human T-cell Lines Specific for Myelin Basic Protein", Proc. Natl. Acad. Sci. (USA), 1992, 89, 137-141 **(Exhibit 98)**;

109. Weinshenker, et al., "Natural History and Treatment of Multiple Sclerosis", Current Opinion in Neurol. and Neurosurgery, 1992, 5, 203-211 **(Exhibit 99)**;

110. Aharoni, et al., "T Suppressor Hybridomas and Interleukin-2-Dependent Lines Induced by Copolymer 1 or by Spinal Cord Homogenate Down-Regulate Experimental Allergic Encephalomyelitis", Eur. J. Immunol., 1993, 23, 17-25 **(Exhibit 100)**;

111. Arnon, et al., "Immunomodulation of Experimental Allergic Encephalomyelitis", Israel J. Med. Sci., 1993, 29, 175-181 **(Exhibit 101)**;

112. Arnon, et al., "On the Existence of Suppressor Cells", Int. Arch. Allergy Immunol., 1993, 100, 2-7 **(Exhibit 102)**;

113. Clinical Trial Protocol No. 9002, Lemmon Co. and Teva Pharmaceutical Industries, Ltd., first patient enrolled June 17, 1993 **(Exhibit 103)**;

114. Francis, "The Current Therapy of Multiple Sclerosis", J. Clin. Pharmacy and Therapeutics, 1993, 18, 77-84 **(Exhibit 104)**;

115. Keleman, et al., "Graft-versus-Host Disease in Bone Marrow Transplantation: Experimental, Laboratory, and Clinical Contributions of the Last Few Years", Int. Arch. Allergy Immunol., 1993, 102, 309-320 **(Exhibit 105)**;

116. Gurevich, "Study of the MHC-competition Between BP and Cop 1 Using Human Cytotoxic T-cell Clones", Israel J. Med. Sci., 1993 (Abstract) **(Exhibit 106)**;

117. Meiner, et al., "The Israeli COP-1 Multicenter Clinical Trial in Exacerbating-remitting Multiple Sclerosis - Two-year Follow-up", in 9th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, Florence (Italy), October-November, 1993, 48 (Abstract) **(Exhibit 107)**;

118. Milo, et al., "Copolymer-1 (COP-1) Regulates Class II MHC Expression and Cytokine Synthesis in the THP-1 Monocyte-Macrophage Cell Line" in The IBC Conference on Multiple Sclerosis, San Diego (USA), December 10, 1993 (Abstract) **(Exhibit 108)**;

119. Sela, "Polymeric Drugs as Immunomodulatory Vaccines Against Multiple Sclerosis", Makromol. Chem. Macromol. Symp., 1993, 70/71, 147-155 **(Exhibit 109)**;

120. Arnon, et al., "Immunospecific Drug Design - Prospects for Treatment of Autoimmune Disease", Therapeutic Immunol., 1994, 1, 65-70 **(Exhibit 110)**;

121. Bansil, et al., "Multiple Sclerosis: Pathogenesis and Treatment", Seminars in Neurol., June 1994, 14(2), 146-153 **(Exhibit 111)**;

122. The COP-1 Multicenter Clinical and Research Group Study, "COP-1 Multicenter Trial in Relapsing Remitting Multiple Sclerosis: 3 Year Follow Up", Abstracts of Symposia and Free Communication, Barcelona (Spain), June 25-29, 1994, 241 (Suppl. 1), 6 **(Exhibit 112)**;

123. Cotton, "Options for Multiple Sclerosis Therapy", J.A.M.A. Medical News & Perspectives, 1994, 272(18), 1393 **(Exhibit 113)**;

124. Dorling, et al., "Prospects for Xenografting", Curr. Opinions Immunol., 1994, 6, 765-769 **(Exhibit 114)**;

125. Fridkis-Hareli, et al., "Copolymer 1 Displaces MBP, PLP and MOG, but Can Not be Displaced by these Antigens from the MHC Class II Binding Site", Department of Chemical Immunology, The Weizmann Institute of Science, 1994 **(Exhibit 115)**;

126. Fridkis-Hareli, et al., "Direct Binding of Myelin Basic Protein and Synthetic Copolymer 1 to Class II Major Histocompatibility Complex Molecules on Living Antigen-Presenting Cells - Specificity and Promiscuity", Proc. Natl. Acad. Sci. USA, 1994, 91, 4872-4876 **(Exhibit 116)**;

127. Fridkis-Hareli, et al., "Specific and Promiscuous Binding of

Synthetic Copolymer 1 to Class II Major Histocompatibility Complex Molecules on Living Antigen Presenting Cells", Israeli Biochem. Soc., 1994, 21-22 (Abstract) **(Exhibit 117)**;

128. Fridkis-Hareli, et al., "Synthetic Copolymer 1 Inhibits the Binding of MBP, PLP and MOG Peptides to Class II Major Histocompatibility Complex Molecules on Antigen Presenting Cells" in Neurochem Mtg., August 14-19, 1994 **(Exhibit 118)**;

129. Fridkis-Hareli, et al., "Synthetic Copolymer 1 Inhibits the Binding of MBP, PLP and MOG Peptides to Class II Major Histocompatibility Complex Molecules on Antigen- Presenting Cells", J. Neurochem., 1994, 63(Suppl. I), 561 **(Exhibit 119)**;

130. Fridkis-Hareli, et al., "Synthetic Copolymer 1 and Myelin Basic Protein do not Require Processing Prior to Binding to Class II Major Histocompatibility Complex Molecules on Living Antigen Presenting Cells", Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot, Israel, 1994. **(Exhibit 120)**;

131. Fridkis-Hareli, et al., "Synthetic Copolymer 1 and Myelin Basic Protein Do Not Require Processing Prior to Binding to Class II Major Histocompatibility Complex Molecules on Living Antigen-Presenting Cells", Cell. Immunol., 1995, 163, 229-236 **(Exhibit 121)**;

132. Fridkis-Hareli, et al., "Synthetic Copolymer 1 and Myelin Basic Protein Do Not Undergo Processing Prior to the Binding to Class II Major Histocompatibility Complex Molecules on

Antigen Presenting Cells", Israeli Immunol. Soc., May 3-4, 1994 (Abstract) **(Exhibit 122)**;

133. Jacobs, et al., "Advances in Specific Therapy for Multiple Sclerosis", Neurol., 1994, 7, 250-254 **(Exhibit 123)**;

134. Johnson, "Experimental Therapy of Relapsing-Remitting Multiple Sclerosis with Copolymer-1", Ann. Neurol., 1994, 36(Suppl.), 115-117 **(Exhibit 124)**;

135. Kott, et al., "COP-1 Increases Suppressor Cells Number in Multiple Sclerosis", Israel Neurological Assoc., December 19-20, 1994, Herzliya (Israel), 17 **(Exhibit 125)**;

136. Mengle-Gaw, "The Major Histocompatibility Complex (MHC)", in Encycl. Molecular Bio. (Oxford Blackwell Science Ltd, 1994) 602-606 **(Exhibit 126)**;

137. Milo, et al., "Additive Effects of COP-1 and IFN-Beta on Immune Responses to Myelin Basic Protein", Neurol., 1994, 44(Suppl. 2), A212 **(Exhibit 127)**;

138. Milo, et al., "Additive Effect of Copolymer-1 and Interferon-β on the Immune Response to Myelin Basic Protein", Assaf Harofeh Medical Center, Sackler School of Medicine, Tel-Aviv University of Maryland School of Medicine, 1994, 22 **(Exhibit 128)**;

139. Milo, et al., "Copolymer-1 and Interferon-β Additively Suppress the Immune Response to Myelin Basic Protein by

Inhibiting Antigen Presentation", J. Neuroimmunol., 1994, 54, 183 (Abstract) **(Exhibit 129)**;

140. Nightingale, et al., "Access to Investigational Drugs for Treatment Purposes", Am. Family Physician, 1994, 50(4), 845-847 **(Exhibit 130)**;

141. Tisch et al., "Antigen-specific immunotherapy: Is it a Real Possibility to Combat T-Cell-Mediated autoimmunity?" Proc. Natl. Acad. Sci. U.S.A., 1994, 91, 437-438; **(Exhibit 131)**;

142. Schlegel, et al., "Prevention of Graft-Versus-Host Disease by Peptides Binding to Class II Major Histocompatibility Complex Molecules", Blood, 1994, 84(8), 2802-2810 **(Exhibit 132)**;

143. Stark, "Expanded Clinical Trials of Treatments for Multiple Sclerosis (MS): Copolymer 1 (COP-1) Treatment Investigational New Drug (IND) Program", Ann. Neurol., 1994, 36, 114-115 **(Exhibit 133)**;

144. Teitelbaum, et al., "Immunological Parameters in a Multicenter Clinical Trial of COP1 in Multiple Sclerosis (MS): A 2-year Follow-up", Neurol., 1994, 44(Suppl. 2), A358 **(Exhibit 134)**;

145. Milo, et al., "Additive Effects of Copolymer-1 and Interferon β-1b on the Immune Response to Myelin Basic Protein", J. Neuroimmunol., 1995, 61, 185-193 **(Exhibit 135)**;

146. O'Connor, et al., "Powders" in The Science and Practice of Pharmacy, Remington, 1995, 2, 1598-1614 **(Exhibit 136)**;

147. Porter, "Coating of Pharmaceutical Dosage Forms," in The Science and Practice of Pharmacy, Remington, 1995, 2, 1650-1659 **(Exhibit 137)**;

148. Reilly, Jr., W.J., "Pharmaceutical Necessities" in The Science and Practice of Pharmacy, Remington 1995, 2, 1380-1416 **(Exhibit 138)**;

149. Schlegel, et al., "Inhibition of Allorecognition and Prevention of Graft-vs-host Disease (GVHD) by GLAT, a Synthetic Polymer with Promiscuous Binding to Murine and Human MHC Class II Molecules", in Am. Soc. Hematology, 37th Annual Meeting, Seattle, WA (USA), December 1-5, 1995, 224a (Abstract) **(Exhibit 139)**;

150. Ben-Nun, et al., "The Autoimmune Reactivity to Myelin Oligodendrocyte Glycoprotein (MOG)in Multiple Sclerosis is Potentially Pathogenic: Effect of Copolymer 1 on MOG-induced Disease", J. Neurol., 1996, 243(Suppl. 1), S14-S22 **(Exhibit 140)**;

151. Johnson, Management of Relapsing/Remitting Multiple Sclerosis with Copolymer 1 (Copaxone)", Chemical Abstracts, 1996, 125, 291993b **(Exhibit 141)**;

152. Sykes, "Immunobiology of Transplantation", Faseb J., 1996, 10, 721-730 **(Exhibit 142)**;

153. Teitelbaum, et al., "Copolymer 1 Inhibits Chronic Relapsing

Experimental Allergic Encephalomyelitis Induced by Proteolipid Protein (PLP) Peptides in Mice and Interferes with PLP-specific T Cell Responses", J. Neuroimmunol., 1996, 64, 209-217 **(Exhibit 143)**;

154. Aharoni, et al., "Studies on the Mechanism and Specificity of the Effect of the Synthetic Random Copolymer GLAT on Graft-versus-Host Disease", Immunol. Letters, 1997, 58, 79-87 **(Exhibit 144)**;

155. Puri et al., "Modulation of the Immune Response in Multiple Sclerosis", J. Immunol., 1997, 158, 2471-2476 **(Exhibit 145)**;

156. Tarcic et al., "Copolymer 1 (Copaxone) from an Idea to a Drug for Treatment of Multiple Sclerosis" Database HCAPLUS on STN, Israel: AN 1997:333270. Kim, Handasa Kim, 1997, 281(14), 16-18 (Abstract) **(Exhibit 146)**;

157. Teitelbaum, et al., "Copolymer 1 from the Laboratory to FDA", Israel J. Med. Sci., 1997, 33, 280-284 **(Exhibit 147)**;

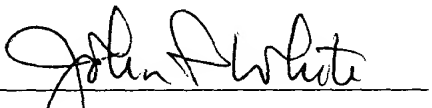
158. Fridkis-Hareli, et al., "Promiscuous Binding of Synthetic Copolymer 1 to Purified HLA-DR Molecules", J. Immunol., 1998, 160, 4386-4397 **(Exhibit 148)**; and

159. Durelli, "Immunotherapeutics of Multiple Sclerosis", Instituto di Clinica delle Malattie del Sistema Nervoso Universita di Torino, 467-475 **(Exhibit 149)**.

If a telephone conference would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

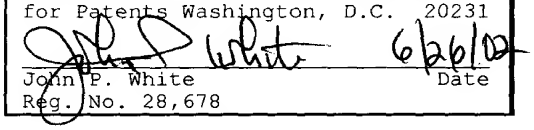
No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any fee is required, authorization is hereby give to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents Washington, D.C. 20231



6/26/02

John P. White
Reg. No. 28,678

Date